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㉛ A novel pharmaceutical composition comprising exifone and water-soluble polymer.

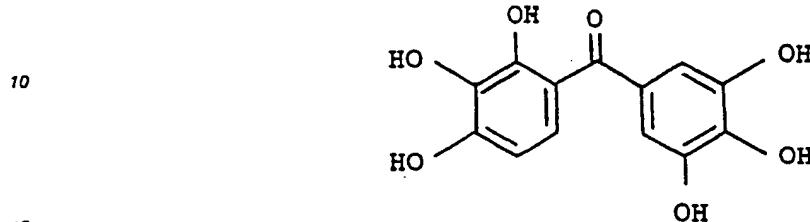
㉜ A pharmaceutical composition comprising exifone and a water-soluble polymer and a process for preparing
it.

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A NOVEL PHARMACEUTICAL COMPOSITION COMPRISING EXIFONE AND WATER-SOLUBLE POLYMER

The present invention relates to a novel pharmaceutical composition comprising exifone and a water-soluble polymer, which improves low absorbability of exifone upon oral administration, and so is useful in the pharmaceutical field.

5 Exifone, which has the structure shown below, is useful as a cerebral metabolic improving agent and effective, for example, in the treatment of senile dementia, cerebrovascular dementia and the like.



[2,3,4,3',4',5'-Hexahydroxybenzophenone]

20 However, exifone is sparingly soluble in water (saturated solubility : about 70-80 µg/ml) and has disadvantage that when it is orally administered as a conventional pharmaceutical composition, its absorption into blood circulation is poor and accordingly its bioavailability is low. Therefore, the advent of a novel pharmaceutical composition which can overcome this drawback has been awaited.

25 The inventors of the present invention found that the above drawback can be overcome by compounding exifone and a water-soluble polymer, and as a result of our intensive investigations, we have completed the present invention.

25 The present invention is the first that has overcome the above drawback of exifone.

30 The novel pharmaceutical composition of the present invention is characterized in that it comprises exifone and a water-soluble polymer. By the coexistence of exifone and a water-soluble polymer the drawback that exifone is sparingly soluble in water is improved and high bioavailability can be attained upon oral administration.

35 The pharmaceutical composition of the present invention may further contain, if necessary, conventional additive(s) used ordinarily in the process of making up pharmaceutical compositions, such as disintegrants, lubricants, excipients, colorants, and so forth. The dosage form is not critical, thus, upon oral administration, the composition can be used, as desired, in the form of powders, fine granules, granules, capsules, tablets, film-coated tablets and so forth.

40 Suitable examples of the water-soluble polymer to be used in this pharmaceutical composition may include those ordinarily used in this field of the art, such as, for example, cellulose derivatives (e.g. hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, etc.), synthetic water-soluble polymer (e.g. polyvinylpyrrolidone, etc.) and the like. Among these, the more preferred one may be cellulose derivatives and the most preferred one may be hydroxypropylmethylcellulose and hydroxypropylcellulose.

45 Suitable disintegrants may include, for example, starch species (e.g. potato starch, corn starch, hydroxypropylstarch, carboxymethylstarch sodium, etc.), cellulose derivatives (e.g. carboxymethylcellulose calcium, carboxymethylcellulose, low substituted hydroxypropylcellulose, etc.) and the like. Suitable lubricants may include, for example, talc, wax species (e.g. white beeswax, hardened oils, etc.), stearic acid species (e.g. stearic acid, magnesium stearate, calcium stearate, etc.) and the like. Suitable excipients may include, for example, sugars (e.g. lactose, sucrose, etc.), starch species (e.g. corn starch, etc.), cellulose derivatives (e.g. microcrystalline cellulose, etc.), inorganic calcium salts (e.g. calcium hydrogen phosphate, calcium sulfate, etc.) and the like and suitable colorants may include, for example, tar dyes and the like. The additives are not limited to the examples mentioned above, but any additives conventionally used in this field of the art may be used.

50 The pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer can be produced by compounding exifone and the above-mentioned water-soluble polymer, if necessary, together with the above-mentioned conventional additive(s), and then converting the mixture to a desired dosage form.

The process for the preparation of the pharmaceutical composition of the present invention by

compounding exifone and water-soluble polymer, etc. may include the process to convert these substances to a solid dispersion composition and the process to mix these substances, and both processes are described in detail hereinbelow.

5

Process to convert the substances to a solid dispersion composition

The pharmaceutical composition of the present invention can be produced by converting exifone to a solid dispersion composition.

10 In order to convert exifone and a water-soluble polymer, if necessary, together with a conventional additive(s) to a solid dispersion composition, any procedure conventionally used in this field of the art may be used.

15 Thus, for instance, said composition can be produced by dissolving exifone in an appropriate organic solvent (e.g. ethanol), then adding to and dissolving or uniformly dispersing in this solution the water-soluble polymer, and after that evaporating the solvent and drying by a conventional method. When the water-soluble polymer is not satisfactorily dissolved in a solvent upon its addition thereto, another organic solvent (e.g. methylene chloride) may be added so as to dissolve it. The solvent may be selected depending upon the kind of the water-soluble polymer employed.

20 When above-mentioned conventional additive(s) are compounded, they may be incorporated into the composition simultaneously as the water-soluble polymer is dispersed in the composition. Alternatively, after preparation of a solid dispersion composition composed of exifone and a water-soluble polymer, said additive(s) may be compounded with said solid dispersion composition.

25 The thus-obtained solid dispersion composition comprising exifone and a water-soluble polymer can be converted to various dosage forms by steps conventionally used in this field of the art, for example, milling sieving, kneading, granulating, tableting, coating, etc. These steps may be carried out in the conventional manner.

Process to mix the substances

30

The pharmaceutical composition of the present invention can be produced by mixing exifone with a water-soluble polymer, if necessary, together with a conventional additive(s).

35 The means of mixing to be used in this process may be any means conventionally employed in this field of the art. For further decreasing the particle size, the resulting mixture may be milled. The milling can be performed by a conventional method.

40 The thus-produced mixture comprising exifone and a water-soluble polymer, etc., if desired, can be converted to various dosage forms by the steps mentioned above for the Process to convert the substances to a solid dispersion composition.

45 This process, Process to mix the substances, is suitable for industrial production because of its being easy to perform.

50 In producing the pharmaceutical composition of the present invention by this process, it is particularly preferable to knead the mixed powder with a suitable kneading solvent and then convert the kneaded matter to the desired dosage form. Suitable kneading solvents may include water, ethanol, and mixtures thereof.

55 The pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer can be produced by the above-mentioned processes. In its production, the kind and the amount of the water-soluble polymer and additive(s) to be used can be selected suitable depending, for example, upon the desired dosage form, the content of exifone therein, the desired dissolution pattern of exifone, and so forth.

When the water-soluble polymer to be used is a cellulose derivative, for instance, the compounding ratio of exifone and the water-soluble polymer is preferably about 1:0.01 to about 1:7 by weight, more preferably 1:0.05 to 1:5 by weight.

When a water-soluble polymer of another kind is used, it is possible for those skilled in the art to determine an appropriate compounding ratio with ease by studying the dissolution pattern, etc. of the composition.

55 In the following, the present invention is explained in detail by Examples.

[I] Process to convert the substances to a solid dispersion composition.

Example 1

Exifone (10 g) was dissolved in ethanol (150 ml). To this solution was added TC-5R (5 g) (trademark, product of Shin-Etsu Chemical; generic name; hydroxypropylmethylcellulose), and the mixture was stirred for achieving dispersion. Furthermore, methylene chloride (50 ml) was added to dissolve TC-5R completely, and after that, the solvent was evaporated.

The residue was dried overnight in vacuo at room temperature, and then milled and sieved (20 mesh) to give a solid dispersion composition.

10

Example 2

A solid dispersion composition was produced from exifone (10 g) and TC-5R (2 g) according to a similar manner to that of Example 1.

15

Example 3

A solid dispersion composition was produced from exifone (10 g) and TC-5R (10 g) according to a similar manner to that of Example 1.

Example 4

25 A solid dispersion composition was produced from exifone (10 g) and TC-5R (30 g) according to a similar manner to that of Example 1.

30

Example 5

A solid dispersion composition was produced from exifone (10 g) and TC-5R (50 g) according to a similar manner to that of Example 1.

35

Example 6

Exifone (10 g) was dissolved in ethanol (150 ml), then TC-5R (5 g) was added to and dispersed in this solution, and methylene chloride (50 ml) was added for complete dissolution of TC-5R. To the solution obtained was added and therein dispersed Explotab (2.5 g) (trademark; product of Kimura Sangyo; generic name : carboxymethylstarch sodium). The solvent was evaporated, and the residue was dried overnight in vacuo at room temperature, then milled and sieved (20 mesh) to give a solid dispersion composition.

45

Example 7

Exifone (10 g) was placed, together with TC-5R (5 g) and Explotab (2.5 g), in a polyethylene bag, and the contents were mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

50

Example 8

Exifone (10 g) and TC-5R (5 g) were placed in a polyethylene bag, and the contents were mixed by shaking it well, then the mixture was milled in a coffee mill for 5 minutes. Explotab (2.5 g) was added to the milled mixture, and the whole was placed in a polyethylene bag and mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 9

After exifone (10 g) and TC-5R (0.5 g) were mixed together in a beaker, the resulting mixture was then kneaded with a 20% aqueous ethanol solution (4 ml) and granulated. After dried in vacuo, the granules were 5 milled in a mortar to an appropriate size and filled into No. 0 capsules to give a capsulated composition.

The formulation per one capsule was as follows :

10

Exifone	200 mg
TC-5R	10 mg
	210 mg

15

Example 10

A capsulated composition having the following formulation was produced from exifone (10 g) and HPC-L (0.5 g) (trademark; product of Nippon Soda; generic name : hydroxypropylcellulose) according to a similar 20 manner to that of Example 9 :

25

Exifone	200 mg
HPC-L	10 mg
	210 mg

30

Example 11

Exifone (10 g) was mixed with TC-5R (1.5 g) in a beaker, and then the mixture was kneaded with a 20% aqueous ethanol solution (5 ml) and granulated. After dried in vacuo, the granules were milled in a mortar and then placed with Explotab (0.35 g) in a polyethylene bag and the mixture was mixed by shaking the 35 bag well to give a TC-5R-treated powder. This mixed powder was filled into No. 0 capsules to give a capsulated composition, each capsule having the following formulation :

40

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
	237 mg

45

Example 12

To the mixed powder comprising TC-5R-treated exifone as obtained according to a similar manner to that of Example 11 was added magnesium stearate (0.15 g) and tabletted by a single punch tabletting 50 machine to give tablets, each having the following formulation :

5

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
Magnesium stearate	3 mg
	240 mg

10

Example 13

A capsulated composition was produced from exifone (10 g) and TC-5R (2.5 g) according to a similar manner to that of Example 9, each capsule having the following formulation :

15

Exifone	200 mg
TC-5R	50 mg
	250 mg

20

Example 14

25

A capsulated composition was produced from exifone (10g), TC-5R (2.5 g) and Explotab (2.5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

30

Exifone	200 mg
TC-5R	50 mg
Explotab	50 mg
	300 mg

35

Example 15

40

A capsulated composition was produced from exifone (10g), TC-5R (5 g) and Explotab (2.5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

45

Exifone	200 mg
TC-5R	100 mg
Explotab	50 mg
	350 mg

50

Example 16

55

A capsulated composition was produced from exifone (10g), TC-5R (10 g) and Explotab (5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

5

Exifone	100 mg
TC-5R	100 mg
Explotab	50 mg
	250 mg

10 Example 17

A capsulated composition was produced from exifone (10 g), TC-5R (30 g) and Explotab (20 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

15

Exifone	50 mg
TC-5R	150 mg
Explotab	100 mg
	300 mg

20

Example 18

25 A capsulated composition was produced from exifone (10 g), TC-5R(50 g) and Explotab (20 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

30

Exifone	50 mg
TC-5R	250 mg
Explotab	100 mg
	400 mg

35

Example 19

40 Exifone (200 g) and TC-5R (100 g) were mixed with each other by shaking well in a polyethylene bag, the mixture was then kneaded with a 20% aqueous ethanol solution(80 ml) as a kneading solvent and granulated using a Planetary mixer for kneading. The granules obtained were dried at 40 °C in vacuo and then milled using Tornado type mill (20 mesh). The powder obtained was mixed with Explotab (27 g) in a polyethylene bag, and the resulting mixture was filled into No. 0 capsules to give a capsulated composition, each having the following formulation :

45

Exifone	200 mg
TC-5R	100 mg
Explotab	27 mg
	327 mg

50

55 Example 20

(1) To the TC-5R-treated powder (before filling into capsules) obtained in Example 19 was added Explotab, Avicel (trademark; product of Asahi Chemical Industry; generic name : microcrystallinecellulose) and magnesium stearate, and then the mixture was tableted in the conventional manner to give tablets each having the following formulation :

5

10

Exifone	200 mg
TC-5R	100 mg
Explotab	37 mg
Avicel	20 mg
Magnesium stearate	3 mg
	360 mg

15

(2) The above tablets were film-coated by a conventional method to give film-coated tablets. The formulation of film coat layer per tablet was as follows :

20

TC-5R	5.4 mg
Polyethylene glycol 6000	0.8 mg
Titanium oxide	1.7 mg
Yellow iron sesquioxide	0.1 mg
	8.0 mg

25

Example 21

Exifone (750 g), TC-5R (375 g), Explotab (101.25 g), lactose (678.75 g) and avicel (678.75 g) were mixed, granulated with an aqueous solution of citric acid (18.75 g), dried and sieved in a conventional method to give granules (2540 g). The granules obtained were mixed with magnesium stearate (33.08 g) and then tabletted in a conventional manner. The tablets thus obtained were film-coated in a conventional method to give film-coated tablets, each having the following formulation :

35

40

45

Core Tablet	
Exifone	40 mg
TC-5R	20 mg
Explotab	5.4 mg
citric acid	1 mg
lactose	35.6 mg
Avicel	36.2 mg
magnesium stearate	1.8 mg
	140 mg

50

55

Film Coat Layer	
TC-5R	3.8 mg
Polyethylene glycol 6000	0.5 mg
titanium oxide	0.56 mg
yellow ferric oxide	0.14 mg
carnauba wax	trace
	5 mg

In the pharmaceutical composition of the present invention the solubility of exifone was markedly

improved as compared with the exifone bulk substance and, when orally administered, a sufficient bioavailability can be obtained.

In the following, for demonstrating the above fact, we set forth the dissolution test results and absorption test results (in dogs) obtained with several representative pharmaceutical compositions produced in accordance with the present invention.

Dissolution test 1

10

[I] Compositions tested

15

Composition A :	The solid dispersion composition obtained in Example 1 (exifone : TC-5R = 1:0.5)
Composition B :	The solid dispersion composition obtained in Example 4 (exifone : TC-5R = 1:3)
Control composition :	Exifone bulk substance (200 mg) filled in a No. 0 capsule

20

[II] Test method

The dissolution percent was determined with passage of the time by the dissolution test method (2nd method) prescribed in the 11th edition of The Pharmacopoeia of Japan. The test conditions were as follows

25

30

Dissolution tester :	Toyama Sangyo model
Sample quantity :	200 mg as exifone
Test solution and its quantity :	1st fluid (pH 1.2), 900 ml
Paddle speed :	100 rpm
Measurement :	uv wavelength 385 nm

35

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

40

45

50

55

Test composition	Time (minutes)	30	60
Composition A		77.0	89.0
Composition B		33.0	48.0
Control composition		11.4	12.4

The above test results clearly shows that in the pharmaceutical composition of the present invention produced by the process to convert the substances to a solid dispersion composition their dissolution patterns were markedly improved as compared with the exifone bulk substance. The drawback of exifone, its sparing solubility, has thus been markedly improved.

5

Dissolution test 2

10 [I] Compostion tested

15	Composition C :	The mixed powder comprising TC-5R-treated exifone obtained in Example 7 (exifone : TC-5R = 1:0,5)
20	Composition D :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 9 (exifone : TC-5R = 1:0,05)
25	Composition E :	The capsule containing a mixed powder comprising HPC-L-treated exifone obtained in Example 10 (exifone:HPC-L = 1:0,05)
30	Composition F :	The tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 12 (exifone : TC-5R = 1:0,15)
	Composition G :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 13 (exifone : TC-5R = 1:0,25)
	Composition H :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 15 (exifone : TC-5R = 1:0,5)
	Control composition :	The same control composition as used in Dissolution test 1.

35 [II] Test method

The same method as used in Dissolution test 1 was used.

40 [III] Test results

The dissolution percent obtained at each measurement time was as follows :

45

50

55

	Time (minutes)	
	30	60
5	Test composition	
10	Composition C	52.1
15	Composition D	78.4
20	Composition E	68.3
25	Composition F	85.8
30	Composition G	80.2
35	Composition H	81.6
40	Control composition	11.4
		12.4

30 The above test results show that in the pharmaceutical compositions of the present invention as produced by the process to mix the substances, whether in the form of mere mixtures or in any of the various dosage forms derived therefrom and in any of the varied mixing ratios, their dissolution patterns were markedly improved as compared with the exifone bulk substance and that, therefore, the drawback of exifone, its sparing solubility, has been markedly improved.

35 Since it has been so far believed that mere mixing of a sparingly soluble medicinal substance with a water-soluble polymer can hardly be expected to result in an improved solubility, the finding that mere mixing may produce a marked improvement as in the pharmaceutical composition of the present invention may be said to be a quite unexpected one.

40 Dissolution test 3

45 [I] Compositions tested

50	Composition I :	The solid dispersion composition obtained in Example 6 filled in No. 0 capsules in an amount of 200 mg as exifone per capsule (exifone : TC-5R = 1:0.5)
55	Composition J :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 19 (exifone : TC-5R = 1:0.5)
	Composition K :	The film-coated tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 21 (exifone : TC-5R = 1:0.5)
	Control composition :	The same control composition as used in Dissolution test 1.

5 [II] Test method

The same method as used in Dissolution test 1 was used

10

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

15

16

20

Time (minutes)	5	15	30	60	120
Test composition	5	15	30	60	120
Composition I	22.9	64.0	77.5	83.5	87.5
Composition J	33.1	60.5	70.8	72.9	81.7
Composition K	13.4	61.8	74.5	79.1	79.1
Control composition	10.4	10.5	11.4	12.4	16.0

25

For demonstrating that an improvement in dissolution behavior can lead to an improvement in absorption upon oral administration, an absorption tests were performed in dogs using the representative pharmaceutical compositions of the present invention. The results are shown below.

30

Absorption test 1

35 [I] Compositions tested

36

Composition I, Composition J and Control composition, as used in Dissolution test 3 were used.

40 [II] Test method

41

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the three-way cross-over method.

42

The dose was 200 mg as exifone per dog (1 capsule of each test composition) and the test compositions were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

47 [III] Test results

50

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}), times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-6}) are shown in the following table. Each data is given in terms of "mean \pm standard error".

55

Time	Plasma concentration (µg/ml)						
	15 min	30 min	60 min	120 min	180 min	240 min	360 min
5 Test composition							
10 Composition I	1.12 ±0.56	2.12 ±0.55	1.08 ±0.18	0.39 ±0.04	0.22 ±0.07	0.15 ±0.07	0.13 ±0.06
15 Composition J	0.99 ±0.45	1.28 ±0.22	0.96 ±0.13	0.54 ±0.12	0.19 ±0.06	0.18 ±0.06	0.15 ±0.07
20 Control composition	0.07 ±0.05	0.15 ±0.07	0.14 ±0.06	0.20 ±0.07	0.11 ±0.07	0.07 ±0.07	0.10 ±0.10
25							

Test compound	C _{max} (µg/ml)	T _{max} (hr)	AUC ₀₋₆ (µg•hr/ml)
Composition I	2.18	0.60	2.86
	±0.55	±0.10	±0.20
Composition J	1.50	0.50	2.59
	±0.36	±0.11	±0.41
Control composition	0.30	1.58	0.69
	±0.06	±0.58	±0.17

Absorption test 2

45

[I] Compositions tested

Composition J and Composition K as used in Dissolution test 3 were used.

50

[II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the two-way cross-over method.

55

The dose was 200 mg as exifone per dog (1 capsule of Composition J and 5 tablets of Composition K) and the test composition were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}), times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-8}) are shown in the following table. Each data is given in terms of "mean \pm standard error".

Time	Plasma concentration ($\mu\text{g}/\text{ml}$)							
	15 min	30 min	60 min	120 min	180 min	240 min	360 min	480 min
Test composition								
Composition J	0.50 ± 0.75	1.20 ± 0.70	1.01 ± 0.36	0.56 ± 0.34	0.42 ± 0.43	0.38 ± 0.46	0.15 ± 0.07	0.13 ± 0.08
Composition K	0.74 ± 0.84	1.47 ± 0.37	0.96 ± 0.06	0.47 ± 0.28	0.20 ± 0.05	0.16 ± 0.07	0.14 ± 0.04	0.13 ± 0.05

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Test compound	C_{max} ($\mu\text{g}/\text{ml}$)	T_{max} (hr)	AUC_{0-8} ($\mu\text{g}\cdot\text{hr}/\text{ml}$)
Composition J	1.52	1.33	3.34
	± 0.39	± 1.35	± 0.88
Composition K	1.66	0.50	2.78
	± 0.34	± 0.15	± 0.42

The above test results clearly show that, as expected on the basis of the results of Dissolution test 3, in the pharmaceutical compositions of the present invention, whether obtained by the process to convert the substances to a solid dispersion composition or by the process to mix the substances, the absorbability into the blood circulation were markedly increased as compared with the exifone bulk substance.

In view of the results of the various tests mentioned above, it is apparent that, in the pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer, both the drawback of exifone, namely, its being sparingly soluble in water, and the low absorbability into blood circulation upon oral administration, which is due to the sparing solubility of exifone, have been improved to a remarkable extent, and so the pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer is very useful.

45 Claims

1. A pharmaceutical composition comprising exifone and a water-soluble polymer.
2. A pharmaceutical composition of claim 1, which comprises a solid dispersion composition comprising exifone and a water-soluble polymer.
3. A pharmaceutical composition of claim 1, which comprises a mixture comprising exifone and a water-soluble polymer.
4. A pharmaceutical composition of claim 2 or claim 3, wherein a water-soluble polymer is cellulose derivatives.
5. A pharmaceutical composition of any of claims 1 to 4, wherein the compounding ratio of exifone and a water-soluble polymer is about 1:0.01 to about 1:7 by weight.
6. A process for preparing a pharmaceutical composition comprising exifone and a water-soluble polymer, which comprises
 - i) converting exifone and a water soluble polymer to a solid dispersion composition, or

ii) mixing exifone with a water-soluble polymer.

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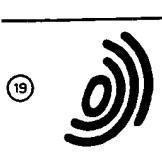
European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 8627

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)						
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim							
X, Y	FR-A-2 377 202 (LABORATORIES PHARMASCIENCE) * Page 1, lines 3-9; page 3, lines 7-16; examples 2,3; claims * ---	1-6	A 61 K 31/12 A 61 K 47/00						
Y	FR-A-2 257 272 (LABORATORIES PHARMASCIENCE ET GAZAVE) * Claims * ---	1-6							
Y	EP-A-0 240 773 (FUJISAWA PHARMACEUTICAL) * Page 2, line 44 - page 3, line 40; claims * ---	1-6							
Y	EP-A-0 137 198 (FUJISAWA PHARMACEUTICAL) * Page 2, line 3 - page 3, line 25; claims * ---	1-6							
Y	DE-A-1 492 034 (MERCK AG) * Page 1, lines 1-3; page 2, line 25 - page 3, line 19; claims * -----	1-6							
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)						
			A 61 K						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>24-01-1989</td> <td>GOETZ G.</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	24-01-1989	GOETZ G.
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THE HAGUE	24-01-1989	GOETZ G.							
<p>CATEGORY OF CITED DOCUMENTS</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document </td> <td style="width: 50%; vertical-align: top;"> T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document </td> </tr> </table>				X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document				
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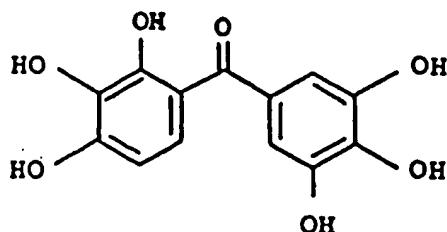
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Description

The present invention relates to a novel pharmaceutical composition comprising a physical mixture comprising exifone and a water-soluble cellulose derivative, which improves low absorbability of exifone upon oral administration, and so is useful in the pharmaceutical field.

Exifone, which has the structure shown below, is useful as a cerebral metabolic improving agent and effective, for example, in the treatment of senile dementia, and cerebrovascular dementia.

10



15

20

[2,3,4,3',4',5'-Hexahydroxybenzophenone]

For example, a pharmaceutical composition for the treatment of functional deficiencies and metabolic irregularities resulting from cerebral and/or peripheral circulatory deficiency which comprises as active ingredient exifone in admixture with the pharmaceutically suitable carrier is described in FR-A-2377202.

25 However, exifone is sparingly soluble in water (saturated solubility : about 70-80 µg/ml) and has disadvantage that when it is orally administered as a conventional pharmaceutical composition, its absorption into blood circulation is poor and accordingly its bioavailability is low. Therefore, the advent of a novel pharmaceutical composition which can overcome this drawback has been awaited.

30 The inventors of the present invention found that the above drawback can be overcome by compounding exifone and a water-soluble cellulose derivative, and as a result of our intensive investigations, we have completed the present invention.

The present invention is the first that has overcome the above drawback of exifone.

35 The novel pharmaceutical composition of the present invention is characterized in that it comprises a physical mixture comprising exifone and a water-soluble cellulose derivative. By the coexistence of exifone and a water-soluble cellulose derivative the drawback that exifone is sparingly soluble in water is improved and high bioavailability can be attained upon oral administration.

40 The pharmaceutical composition of the present invention may further contain, if necessary, conventional additive(s) used ordinarily in the process of making up pharmaceutical compositions, such as disintegrants, lubricants, excipients and colorants. The dosage form is not critical, thus, upon oral administration, the composition can be used, as desired, in the form of powders, fine granules, granules, capsules, tablets and film-coated tablets.

45 Suitable examples of the water-soluble cellulose derivative to be used in this pharmaceutical composition are those ordinarily used in this field of the art, such as, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose. Among these, the more preferred cellulose derivatives may be hydroxypropylmethylcellulose and hydroxypropylcellulose.

50 Suitable disintegrants may include, for example, starch species (e.g. potato starch, corn starch, hydroxypropylstarch, carboxymethylstarch sodium,), cellulose derivatives (e.g. carboxymethylcellulose calcium, carboxymethylcellulose, low substituted hydroxypropylcellulose). Suitable lubricants may include, for example, talc, wax species (e.g. white beeswax, hardened oils,), stearic acid species (e.g. stearic acid, magnesium stearate, calcium stearate,), Suitable excipients may include, for example, sugars (e.g. lactose, sucrose,), starch species (e.g. corn starch,), cellulose derivatives (e.g. microcrystalline cellulose,), inorganic calcium salts (e.g. calcium hydrogen phosphate, calcium sulfate,) and suitable colorants may include, for example, tar dyes.

55 The pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative can be produced by compounding exifone and the above-mentioned water-soluble cellulose derivative, if necessary, together with the above-mentioned conventional additive(s), and then converting the mixture to a desired dosage form.

The process for the preparation of the pharmaceutical composition of the present invention by

compounding exifone and water-soluble cellulose derivative is the process to mix these substances, and the process is described in detail hereinbelow.

Process to mix the substances

5

The pharmaceutical composition of the present invention can be produced by mixing exifone with a water-soluble cellulose derivative, if necessary, together with a conventional additive(s).

10

The means of mixing to be used in this process may be any means conventionally employed in this field of the art. For further decreasing the particle size, the resulting mixture may be milled. The milling can be performed by a conventional method.

15

The thus-produced mixture comprising a physical mixture comprising exifone and a water-soluble cellulose derivative, if desired, can be converted to various dosage forms by the steps conventionally used in this field of the art, for example, milling sieving, kneading, granulating, tableting and coating. These steps may be carried out in the conventional manner.

20

This process, Process to mix the substances, is suitable for industrial production because of its being easy to perform.

In producing the pharmaceutical composition of the present invention by this process, it is particularly preferable to knead the mixed powder with a suitable kneading solvent and then convert the kneaded matter to the desired dosage form. Suitable kneading solvents may include water, ethanol, and mixtures thereof.

25

The pharmaceutical composition of the present invention which comprises exifone and a can be produced by the above-mentioned process. In its production, the kind and the amount of the water-soluble cellulose derivative and additive(s) to be used can be selected suitable depending, for example, upon the desired dosage form, the content of exifone therein, the desired dissolution pattern of exifone, and so forth.

30

The compounding ratio of exifone and the cellulose derivative is preferably about 1:0.01 to about 1:7 by weight, more preferably 1:0.05 to 1:5 by weight.

In the following, the present invention is explained in detail by Examples.

(I) Process to mix the substances

30 Example 1

Exifone (10 g) was placed, together with TC-5R (5 g) (trademark, product of Shin-Etsu Chemical; generic name; hydroxypropylmethylcellulose) and Explotab (2.5 g) (trademark; product of Kimura Sangyo; generic name: carboxymethylstarch sodium) in a polyethylene bag, and the contents were mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 2

Exifone (10 g) and TC-5R (5 g) were placed in a polyethylene bag, and the contents were mixed by shaking it well, then the mixture was milled in a coffee mill for 5 minutes. Explotab (2.5 g) was added to the milled mixture, and the whole was placed in a polyethylene bag and mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 3

45

After exifone (10 g) and TC-5R (0.5 g) were mixed together in a beaker, the resulting mixture was then kneaded with a 20% aqueous ethanol solution (4 ml) and granulated. After dried in vacuo, the granules were milled in a mortar to an appropriate size and filled into No. 0 capsules to give a capsulated composition.

The formulation per one capsule was as follows :

50

Exifone	200 mg
TC-5R	10 mg
	210 mg

55

Example 4

5 A capsulated composition having the following formulation was produced from exifone (10 g) and HPC-L (0.5 g) (trademark; product of Nippon Soda; generic name : hydroxypropylcellulose) according to a similar manner to that of Example 3 :

Exifone	200 mg
HPC-L	10 mg
	210 mg

10

Example 5

15 Exifone (10 g) was mixed with TC-5R (1.5 g) in a beaker, and then the mixture was kneaded with a 20% aqueous ethanol solution (5 ml) and granulated. After dried in vacuo, the granules were milled in a mortar and then placed with Explotab (0.35 g) in a polyethylene bag and the mixture was mixed by shaking the bag well to give a TC-5R-treated powder. This mixed powder was filled into No. 0 capsules to give a capsulated composition, each capsule having the following formulation :

20

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
	237 mg

25

Example 6

30 To the mixed powder comprising TC-5R-treated exifone as obtained according to a similar manner to that of Example 11 was added magnesium stearate (0.15 g) and tabletted by a single punch tabletting machine to give tablets, each having the following formulation :

35

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
Magnesium stearate	3 mg
	240 mg

40

Example 7

45 A capsulated composition was produced from exifone (10 g) and TC-5R (2.5 g) according to a similar manner to that of Example 9, each capsule having the following formulation :

50

Exifone	200 mg
TC-5R	50 mg
	250 mg

Example 8

55 A capsulated composition was produced from exifone (10 g), TC-5R (2.5 g) and Explotab (2.5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

5

Exifone	200 mg
TC-5R	50 mg
Explotab	50 mg
	300 mg

Example 9

10

A capsulated composition was produced from exifone (10 g), TC-5R (5 g) and Explotab (2.5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

15

Exifone	200 mg
TC-5R	100 mg
Explotab	50 mg
	350 mg

20

Example 10

A capsulated composition was produced from exifone (10 g), TC-5R (10 g) and Explotab (5 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

25

30

Exifone	100 mg
TC-5R	100 mg
Explotab	50 mg
	250 mg

Example 11

35

A capsulated composition was produced from exifone (10 g), TC-5R (30 g) and Explotab (20 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

40

Exifone	50 mg
TC-5R	150 mg
Explotab	100 mg
	300 mg

45

Example 12

A capsulated composition was produced from exifone (10 g), TC-5R (50 g) and Explotab (20 g) according to a similar manner to that of Example 5, each capsule having the following formulation :

50

55

Exifone	50 mg
TC-5R	250 mg
Explotab	100 mg
	400 mg

Example 13

Exifone (200 g) and TC-5R (100 g) were mixed with each other by shaking well in a polyethylene bag, the mixture was then kneaded with a 20% aqueous ethanol solution (80 ml) as a kneading solvent and granulated using a Planetary mixer for kneading. The granules obtained were dried at 40°C in vacuo and then milled using Tornado type mill (20 mesh). The powder obtained was mixed with Explotab (27 g) in a polyethylene bag, and the resulting mixture was filled into No. 0 capsules to give a capsulated composition, each having the following formulation :

10

Exifone	200 mg
TC-5R	100 mg
Explotab	27 mg
	327 mg

15

Examples 14

20

(1) To the TC-5R-treated powder (before filling into capsules) obtained in Example 13 was added Explotab, Avicel (trademark; product of Asahi Chemical Industry; generic name : microcrystalline cellulose) and magnesium stearate, and then the mixture was tableted in the conventional manner to give tablets each having the following formulation :

25

Exifone	200 mg
TC-5R	100 mg
Explotab	37 mg
Avicel	20 mg
Magnesium stearate	3 mg
	360 mg

30

(2) The above tablets were film-coated by a conventional method to give film-coated tablets. The formulation of film coat layer per tablet was as follows :

35

TC-5R	5.4 mg
Polyethylene glycol 6000	0.8 mg
Titanium oxide	1.7 mg
Yellow iron sesquioxide	0.1 mg
	8.0 mg

40

Example 15

45

Exifone (750 g), TC-5R (375 g), Explotab (101.25 g), lactose (678.75 g) and avicel (678.75 g) were mixed, granulated with an aqueous solution of citric acid (18.75 g), dried and sieved in a conventional method to give granules (2540 g). The granules obtained were mixed with magnesium stearate (33.08 g) and then tabletted in a conventional manner. The tablets thus obtained were film-coated in a conventional method to give film-coated tablets, each having the following formulation :

50

55

5	Core Tablet	
10	Exifone	40 mg
	TC-5R	20 mg
	Explotab	5.4 mg
	citric acid	1 mg
	lactose	35.6 mg
	Avicel	36.2 mg
	magnesium stearate	1.8 mg
		140 mg

15	Film Coat Layer	
20	TC-5R	3.8 mg
	Polyethylene glycol 6000	0.5 mg
	titanium oxide	0.56 mg
	yellow ferric oxide	0.14 mg
	carnauba wax	trace
		5 mg

25 In the pharmaceutical composition of the present invention the solubility of exifone was markedly improved as compared with the exifone bulk substance and, when orally administered, a sufficient bioavailability can be obtained.

30 In the following, for demonstrating the above fact, we set forth the dissolution test results and absorption test results (in dogs) obtained with several representative pharmaceutical compositions produced in accordance with the present invention.

35 Dissolution test 1

[I] Composition tested

40 Composition A : The mixed powder comprising TC-5R-treated exifone obtained in Example 1 (exifone : TC-5R = 1:0.5)

Composition B : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 3 (exifone : TC-5R = 1:0.05)

Composition C : The capsule containing a mixed powder comprising HPC-L-treated exifone obtained in Example 4 (exifone:HPC-L = 1:0.05)

45 Composition D : The tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 6 (exifone : TC-5R = 1:0.15)

Composition E : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 7 (exifone : TC-5R = 1:0.25)

50 Composition F : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 9 (exifone : TC-5R = 1:0.5)

Control composition : The same control composition as used in Dissolution test 1.

[II] Test method

55

The dissolution percent was determined with passage of the time by the dissolution test method (2nd method) prescribed in the 11th edition of The Pharmacopoeia of Japan. The test conditions were as follows :

55

5

Dissolution tester	Toyama Sangyo model
Sample quantity	200 mg as exifone
Test solution and its quantity	1st fluid (pH 1.2), 900 ml
Paddle speed	100 rpm
Measurement	uv wavelength 385 nm

10

[III] Test results

15

The dissolution percent obtained at each measurement time was as follows :

20

Time (minutes)	30	60
Test composition		
Composition <i>A</i>	52.1	68.1
Composition <i>B</i>	78.4	83.1
Composition <i>C</i>	68.3	71.7
Composition <i>D</i>	85.8	88.6
Composition <i>E</i>	80.2	93.8
Composition <i>F</i>	81.6	84.9
Control composition	11.4	12.4

25

The above test results show that in the pharmaceutical compositions of the present invention as produced by the process to mix the substances, whether in the form of mere mixtures or in any of the various dosage forms derived therefrom and in any of the varied mixing ratios, their dissolution patterns were markedly improved as compared with the exifone bulk substance and that, therefore, the drawback of exifone, its sparing solubility, has been markedly improved.

30

Since it has been so far believed that mere mixing of a sparingly soluble medicinal substance with a water-soluble cellulose derivative can hardly be expected to result in an improved solubility, the finding that mere mixing may produce a marked improvement as in the pharmaceutical composition of the present invention may be said to be a quite unexpected one.

Dissolution test 2

35

[I] Compositions tested

Composition G : The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 13 (exifone : TC-5R = 1:0.5)
 Composition H : The film-coated tablet comprising a mixed powder comprising TC-5R-treated

exifone obtained in Example 15 (exifone : TC-5R = 1:0.5)
 Control composition : The same control composition as used in Dissolution test 1.

[II] Test method

5

The same method as used in Dissolution test 1 was used.

[III] Test results

10 The dissolution percent obtained at each measurement time was as follows :

15 Test composition	Time (minutes)				
	5	15	30	60	120
20 Composition G	33.1	60.5	70.8	72.9	81.7
Composition H	13.4	61.8	74.5	79.1	79.1
25 Control composition	10.4	10.5	11.4	12.4	16.0

For demonstrating that an improvement in dissolution behavior can lead to an improvement in absorption upon oral administration, an absorption tests were performed in dogs using the representative pharmaceutical compositions of the present invention. The results are shown below.

Absorption test 1

[I] Compositions tested

35

Composition G and Control composition, as used in Dissolution test 2 were used.

[II] Test method

40 The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the three-way cross-over method.

The dose was 200 mg as exifone per dog (1 capsule of each test composition) and the test compositions were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

45

[III] Test results

50 Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}),times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-6}) are shown in the following table.

Each data is given in terms of "mean \pm standard error".

55

Time	Plasma concentration ($\mu\text{g}/\text{ml}$)						
	15 min	30 min	60 min	120 min	180 min	240 min	360 min
Test composition							
Composition 6	0.99 ±0.45	1.28 ±0.22	0.96 ±0.13	0.54 ±0.12	0.19 ±0.06	0.18 ±0.06	0.15 ±0.07

Test compound	C_{max} ($\mu\text{g}/\text{ml}$)	T_{max} (hr)	AUC_{0-6} ($\mu\text{g}\cdot\text{hr}/\text{ml}$)
Composition 6	1.50 ±0.36	0.50 ±0.11	2.59 ±0.41
Control composition	0.30 ±0.06	1.58 ±0.58	0.69 ±0.17

Absorption test 2

[I] Compositions tested

Composition G and Composition H as used in Dissolution test 2 were used.

50 [II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the two-way cross-over method.

55 The dose was 200 mg as exitone per dog (1 capsule of Composition G and 5 tablets of Composition H) and the test composition were administered orally. After administration, blood samples were taken from the antecubital vein with passage of the time and immediately assayed for exitone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}), times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-8}) are shown in the following table.
Each data is given in terms of "mean \pm standard error".

5

10

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35

Time Test compo- sition	Plasma concentration ($\mu\text{g}/\text{ml}$)							
	15 min	30 min	60 min	120 min	180 min	240 min	360 min	480 min
Composition G	0.50	1.20	1.01	0.56	0.42	0.38	0.15	0.13
Composition H	± 0.75	± 0.70	± 0.36	± 0.34	± 0.43	± 0.46	± 0.07	± 0.08
Composition G	0.74	1.47	0.96	0.47	0.20	0.16	0.14	0.13
Composition H	± 0.84	± 0.37	± 0.06	± 0.28	± 0.05	± 0.07	± 0.04	± 0.05

Test compound	C_{max} ($\mu\text{g}/\text{ml}$)	T_{max} (hr)	AUC_{0-8} ($\mu\text{g}\cdot\text{hr}/\text{ml}$)
Composition G	1.52	1.33	3.34
Composition G	± 0.39	± 1.35	± 0.88
Composition H	1.66	0.50	2.78
Composition H	± 0.34	± 0.15	± 0.42

The above test results clearly show that, as expected on the basis of the results of Dissolution test 2, in the pharmaceutical compositions of the present invention, obtained by the process to mix the substances, the absorbability into the blood circulation were markedly increased as compared with the exifone bulk substance.

In view of the results of the various tests mentioned above, it is apparent that, in the pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative, both the drawback of exifone, namely, its being sparingly soluble in water, and the low absorbability into blood circulation upon oral administration, which is due to the sparing solubility of exifone, have been improved to a remarkable extent, and so the pharmaceutical composition of the present invention which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative is very useful.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition which comprises a physical mixture comprising exifone and a water-soluble cellulose derivative.
2. A pharmaceutical composition of claim 1, wherein the compounding ratio of exifone and the water-soluble cellulose derivative is 1:0.01 to 1:7 by weight.
3. A process for preparing a pharmaceutical composition comprising exifone and a cellulose derivative,

which comprises physical mixing exifone with a water-soluble cellulose derivative.

Claims for the following Contracting State : ES

5 1. A process for preparing a pharmaceutical composition comprising exifone and a cellulose derivative, which comprises physical mixing exifone with a water-soluble cellulose derivative.

10 2. Process according to claim 1, which comprises physical mixing exifone with a cellulose derivative in a compounding ratio from 1:0.01 to 1:7 by weight.

10 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

15 1. Eine pharmazeutische Zusammensetzung, die eine physikalische Mischung, umfassend Exifone und ein wasserlösliches Cellulose-Derivat, umfasst.

20 2. Eine pharmazeutische Zusammensetzung aus Anspruch 1, worin das Mischungsverhältnis von Exifone und dem wasserlöslichen Cellulose-Derivat 1:0.01 bis 1:7 Gew.-Anteile beträgt.

25 3. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend Exifone und ein Cellulose-Derivat, das physikalisches Mischen von Exifone mit einem wasserlöslichen Cellulose-Derivat umfasst.

Patentansprüche für folgenden Vertragsstaat : ES

25 1. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend Exifone und ein Cellulose-Derivat, das physikalisches Mischen von Exifone mit einem wasserlöslichen Cellulose-Derivat umfasst.

30 2. Verfahren nach Anspruch 1, das physikalisches Mischen von Exifone mit einem Cellulose-Derivat in einem Mischungsverhältnis von 1:0.01 bis 1:7 Gew.-Anteilen umfasst.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

35 1. Composition pharmaceutique comportant un mélange physique de l'exifone et un dérivé de la cellulose soluble dans l'eau.

40 2. Composition pharmaceutique selon la revendication 1 dans laquelle le rapport composant de l'exifone et du dérivé de la cellulose soluble dans l'eau est entre 1:0,01 à 1:7 en poids.

45 3. Procédé pour réparer une composition pharmaceutique comportant de l'exifone et un dérivé de la cellulose, qui comporte mélangé physiquement de l'exifone avec un dérivé de la cellulose soluble dans l'eau.

Revendications pour l'Etat contractant suivant : ES

50 1. Procédé pour la préparation d'une composition pharmaceutique comportant de l'exifone et un dérivé de la cellulose, qui comporte mélangé physiquement de l'exifone avec un dérivé de la cellulose soluble dans l'eau.

55 2. Procédé selon la revendication 1, comportant mélangé physiquement de l'exifone avec un dérivé de la cellulose dans un rapport composant de 1:0,01 à 1:7 en poids.